UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,998	09/19/2003	Andrei Laikhter	013670-9004 US00	1003

52229 7590 01/16/2009

MICHAEL BEST & FRIEDRICH LLP
ONE SOUTH PINCKNEY STREET
P.O. BOX 1806
MADISON, WI 53701

EXAMINER	
STAPLES, MARK	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
01/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,998	LAIKHTER ET AL.	
	Examiner	Art Unit	
	Mark Staples	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-50* is/are rejected.

7)☒ Claim(s) *50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/21/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/17/2008 has been entered.

2. Applicant's amendment of claim 37 in the paper filed on 10/15/2008 is acknowledged.

Claims 37-50 are pending and at issue.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections and Rejections that are Withdrawn

3. The objection to the title is withdrawn in light of amendment of the title per Applicant's acceptance of the suggestion for the title given in the prior Office action. The title has been changed to that below.

METHODS OF DETECTING FLUORESCENCE WITH ANTHRAQUINONE QUENCHER DYES

Claim Rejections Withdrawn - 35 USC § 102(b)

4. The rejection of claims 37-47, 49, and 50 under 35 U.S.C. 102(b) as being anticipated by Batz et al. (2000) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

Claim Rejections Withdrawn - 35 USC § 103(a)

5. The rejection of claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Batz et al. and further in view of Jenne et al. (2002) is withdrawn. Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection, necessitated by amendment.

New Rejections Necessitated by Amendment

Claim Interpretation

6. As the specification does not provide a definition of phosphodiester backbone, this term has been interpreted according to the accepted meaning of the art as being a biological structure inherently found in nucleic acids. That this meaning is accepted in the art is evidenced by Encyclopædia Britannica (2008, previously cited).

> "nucleic acid." Encyclopædia Britannica. 2008. Encycloædia Britannica Online. 11 July 2008 <http://www.search.eb.com/eb/article-256731>

New Claim Rejections 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

8. Claims 37-40 are rejected under 35 U.S.C. 102(e) as being anticipated by Jones et al. (United States Patent 7,122,383 filed March 18, 2002 and issued October 17, 2006).

Regarding claims 37 and 40, Jones et al. teach methods of detecting fluorescence of a fluorophore in a system (entire patent),

comprising the fluorophore and a nucleic acid polymer having a phosphodiester backbone which can be a target biological agent (see claims 1, 7, and 17),

comprising an quencher which can be the anthraquinone quencher conjugated/covalently bound to polymer 1 (see column 6 lines 34-39) which can be a recognition element which is a nucleic acid or an oligonucleotide (see claim 17), comprising detecting the reduction in fluorescence of the fluorophore in the system (see claims 1-20).

Regarding claim 38, Jones et al. teach that the change in fluorescence is correlated with the spatial relationship between the quencher and the fluorophore (entire patent, especially column 12 lines 15-21).

Regarding claim 39, Jones et al. teach the fluorophore can be a polymer 2 which fluoresces intrinsically or has a fluorophore attached and which then binds/attaches to

polymer 1 to be quenched by the anthraquinone quencher conjugated/covalently bound to polymer 1 (see column 5 line 56 to column 7 lines 46).

New Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 37-47, 49, and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ju et al. (1995), Batz et al. (United States Patent No. 6,117,973 issued September 12, 2000, previously cited), and Schuster (2000).

Regarding claim 37, Ju et al. teach methods of detecting fluorescence of a fluorophore in a system (entire article)

comprising the fluorophore which is 5-carboxyfluorescein (FAM) and a nucleic acid polymer having a phosphodiester backbone which are oligonucleotides (see Figure 1),

comprising an quencher which can be the dyes 2',7'-dimethoxy-4',5'-dichloro-6-carboxyfluorescein (JOE or J), N,N,N',N'-tetramethyl-6-carboxyrhodamine (TAMRA or T), or 6-carboxy-X-rhodamine (ROX or R) covalently bound to the polymer, comprising detecting the fluorescence of the system.

Regarding claim 37, Ju et al. teach quenchers but do not specifically teach an anthraquinone quencher.

Regarding claim 37, Batz et al. teach a method of detecting fluorescence of a fluorophore in a system comprising the fluorophore and a nucleic acid polymer comprising an anthraquinone quencher covalently bound thereto, comprising detecting the fluorescence of the system (see column 21 lines 42-63).

Regarding claim 37, Batz et al. teach an anthraquinone quencher covalently bound to a peptide nucleic acid polymer but do not specifically teach that the an anthraquinone quencher is covalently bound to a polymer with a phosphodiester backbone.

Regarding claim 38, Batz et al. teach wherein a change in fluorescence of the system is correlated with a change in the spatial relationship between the quencher and the fluorophore (see column 21 lines 42-63 and column 22 lines 1-20).

Regarding claim 39, Batz et al. teach wherein the fluorophore is attached to the nucleic acid polymer comprising the anthraquinone quencher (in a PNA hairpin system, see column 21 lines 42-63).

Regarding claim 40, Batz et al. teach wherein the fluorophore and anthraquinone quencher are attached to the polymer such that the fluorescence of the fluorophore is reduced (see column 22 lines 1-20).

Regarding claim 41, Batz et al. teach wherein the nucleic acid polymer forms a random-coil conformation when the nucleic acid polymer is unhybridized, such that the fluorescence of the fluorophore is reduced (see column 21 lines 42-63 and column 22 lines 1-20).

Regarding claim 42, Batz et al. teach wherein the system is a system for detecting a target nucleic acid having a sequence complimentary to at least a portion of the nucleic acid polymer, hybridization of the nucleic acid polymer to the target nucleic acid causing a change in fluorescence indicative of the presence of the target nucleic acid (see column 23 lines 9-27 and see Figure 6).

Regarding claim 43, Batz et al. teach wherein the nucleic acid polymer comprises a self- complimentary sequence and wherein the quencher and the fluorophore are attached to the nucleic acid polymer such that the fluorescence of the fluorophore is

quenched by the anthraquinone quencher when the nucleic acid polymer undergoes intramolecular base pairing (see column 23 lines 9-50 and see Figure 6).

Regarding claim 44, Batz et al. teach wherein hybridization of the polymer to the target nucleic acid results in an increase in fluorescence of the fluorophore (see column 23 lines 9-50 and see Figure 6).

Regarding claim 45, Batz et al. teach wherein the fluorophore is attached to a second nucleic acid polymer, and wherein the first and second nucleic acid polymers hybridize to two adjacent regions of the target nucleic acid such that when both polymers hybridize to the target nucleic acid the fluorescence of the fluorophore is reduced (see Figure 3 and its description in column22 lines 56-61).

Regarding claim 46, Batz et al. teach wherein the fluorophore is attached to a second nucleic acid polymer complimentary to the first nucleic acid polymer, such that when the first and second nucleic acid are hybridized, the fluorescence of the fluorophore is reduced (see column 23 lines 51-63 and Figure 7).

Regarding claim 47, Batz et al. teach wherein the system further comprises a target nucleic acid comprising a sequence that hybridizes to the first or second nucleic acid polymer, hybridization of the target nucleic acid to the first or second nucleic acid polymer causing an increase in fluorescence (see column 23 lines 51-63 and Figure 7).

Regarding claim 49, Batz et al. teach wherein the system is a PCR reaction, mixture wherein synthesis of product, which is an amplicon, results in a change in fluorescence (see column 23 line 22-27).

Regarding claim 50, Batz et al. teach compounds of amended instant claim 50 as follows.

Batz et al teach at least two compounds according to formula VIa (see claim 7) where:

n = m = 0;

$(R)_1$ = hydrogen;

$(R)_k$ = NHR';

R' = OR'; and

R' = PO_3^{2-} (1st compound) or = PO_2^- (second compound).

Batz et al teach additional compounds according to formula VIa (see claim 7) where:

n = m = 0;

$(R)_1$ = hydrogen;

$(R)_k$ = N(R''R');

R' = OR';

R' = PO_3^{2-} or = PO_2^-; and

R'' is any of the groups other than acetyl that can covalently bind to nitrogen (as listed in claim 7).

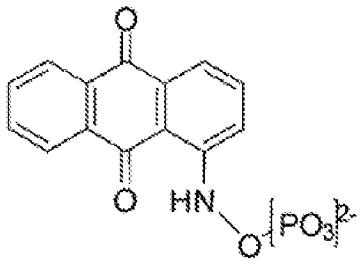
The first and second compounds are compounds of instant claim 1 where:

R_1 = R_{14} = R_{15} = R_6 = R_7 = R_8 = R_9 = R_{10} = hydrogen;

$R_1 = R_{14} = R_{15}$ = hydrogen; and

$X = PO_3^{2-}$ (first compound) or = PO_2^- (second compound).

The structure of the first compound is given below.



The additional compounds taught by Batz et al. are compounds of the instant claim 50 where:

$R_1 = R_{14} = R_{15} = R_7 = R_8 = R_9 = R_{10}$ = hydrogen;

$R_1 = R_{14} = R_{15}$ = hydrogen;

$X = PO_3^{2-}$ or = PO_2^- ; and

R_6 = is any of the groups other than acetyl that can covalently bind to nitrogen (as recited instant claim 50).

Regarding claim 37, Schuster teaches methods of detecting fluorescence of a fluorophore in a system (entire article),

comprising a fluorophore which is a fluorescer and a nucleic acid polymer having a phosphodiester backbone which is DNA (see 3rd full paragraph on p. 258),

comprising quenchers which are fluorescent electron acceptors covalently bound to a nucleic acid polymer having a phosphodiester backbone which is DNA (see 3rd full paragraph on p. 258),

comprising detecting the fluorescence of the system (see 4th and 5th paragraphs on p. 258),

and teaches anthraquinones covalently attached to DNA (see Abstract and last sentence of the 5th paragraph on p. 254).

Regarding claim 37, Schuster suggests but does not specifically teach anthraquinones as quenchers.

Ju et al. teach energy transfer methods comprising both fluorophores and quenchers covalently bound to nucleic acid polymers with phosphodiester backbones which form duplexes through hybridization of two oligodeoxynucleotides to form a type of DNA/DNA complex. Ju et al. also teach that the principle that one of the dyes in the energy transfer is a quencher (see 2nd and third paragraphs on p. 4347). Ju et al. do not specifically teach anthraquinone quenchers.

Batz et al. teach energy transfer methods comprising fluorophores covalently bound to nucleic acid polymers and anthraquinone quenchers covalently bound to peptide nucleic acids polymers (PNA) which form duplexes through hybridization with deoxyribonucleic acid polymers (DNA) to form PNA/DNA hybrid complex. As with Ju et al., Batz et al. also teach the principle that one of the dyes in the energy transfer is a quencher (see Figures 1-4). Batz et al. also teach energy transfer methods comprising

fluorophores and quenchers covalently bound to nucleic acid polymers which form DNA/DNA complexes (see column 4 lines 37-43) and suggest but do not specifically the anthraquinone quencher covalently bound to a DNA polymer having a phosphodiester backbone. Batz et al. teaches anthraquinones as quenchers.

Schuster teaches energy transfer methods comprising both fluorophores and quenchers covalently bound to nucleic acid polymers with phosphodiester backbones which form duplexes through hybridization of two oligodeoxynucleotides to from a type of DNA/DNA complex. Schuster teaches anthraquinones covalently bound to DNA polymers having phosphodiester backbones. Schuster suggests but does not specifically teach anthraquinones as quenchers/acceptors.

Ju et al., Batz et al., and Schuster teach energy transfer methods using quenchers covalently bound to polymers and teach DNA as polymers which can be used with a pair of a fluorophore and a quencher. Thus it would have been obvious to one skilled in the art to substitute the anthraquinone quenchers as taught by Batz et al. and Schuster for a quencher taught by Ju et al. in order to achieve the predictable result of an anthraquinone quencher covalently bound to DNA polymers with phosphodiester backbones. The motivation to do so is provided by Batz et al. who teach that anthraquinones are preferred quenchers (see column 16 lines 20 and 21). One would have reasonably expected success since Schuster teaches the ease of covalently attaching anthraquinones to DNA by teaching: “The synthesis of DNA oligomers [polymers] containing a linked anthraquinone group proceeds smoothly from the phosphoramidite using solid-phase methods” (see 1st sentence of last paragraph on p.

254). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

12. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ju et al., Batz et al., and Schuster as applied to claim 37 above, and further in view of Jenne et al. (United States Patent No. 6,451,535 issued September 17, 2002, previously cited).

Ju et al., Batz et al., and Schuster teach as noted above.

Ju et al., Batz et al., and Schuster do not specifically teach separation of an anthraquinone quencher from a fluorophore by cleaving an RNAse restriction site between them.

Regarding claims 48, Jenne et al. teach wherein the system is a system for measuring RNAse activity, wherein the nucleic acid polymer is a ribonucleic acid polymer comprising the fluorophore attached thereto, wherein the ribonucleic acid polymer comprises an RNAse restriction site between the quencher and the fluorophore, a change in fluorescence indicating the presence of RNAse which is ribonuclease P (see Figure 1 and see column 2 lines 32-40).

Jenne et al. do not teach an anthraquinone quencher.

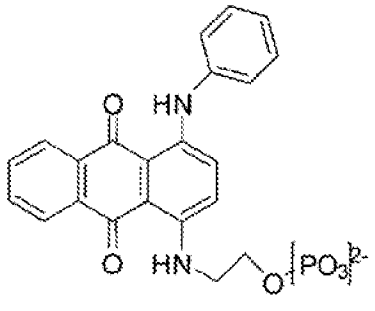
Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Jenne et al. by substituting an anthraquinone quencher as suggested by Ju et al., Batz et al., and Schuster with a reasonable expectation of success. The motivation to do so is provided

by Batz et al. who teach that anthraquinones are preferred acceptors/quenchers in quencher and fluorophore pairs (see column 15 line 44) and the teaching of Jenne et al. that quencher and fluorophore pairs can be used used to monitor RNAse activity (entire patent, especially Figures 1-4 and see column 2 lines 32-40) for direct, reproducible, highly sensitive, and simple detection of mRNA in cell extracts (see column 2 lines 1-19). Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Allowable Subject Matter

13. The elected specie of claim 50 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

14. The following is a statement of reasons for the indication of allowable subject matter: no prior art was found which teaches or fairly suggests the elected specie of the compound shown below. A structure search for the compound was conducted and no prior was found which taught or fairly suggested this compound.



Conclusion

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark Staples whose telephone number is (571) 272-9053. The examiner can normally be reached on Monday through Thursday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Mark Staples
/M. S./
Examiner, Art Unit 1637
January 11, 2009

/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637

January 15, 2009